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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,458	10/20/2003	Alfred M. Ajami	3287.1000-003	4844

21005 7590 06/09/2004

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EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,458	AJAMI ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, definition of R1, R2 as $-N^{+}HR6R7$ has no antecedent basis in the definition of R2 where only $-N^{+}HR6R7X^{-}$ is recited. The rejection is applicable to claims dependent on claim 1.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brana I (4204063, PTO-1449) in view of Brana II (5420137, PTO-1449), Berge (Journal of Pharmaceutical Sciences, 1977, 66(1); 1-19) and Zee-Cheng (4614820).

Brana I generically discloses a N-aminoalkyl-naphthalimide compound and its pharmaceutically acceptable salt as anti-tumor agent (column 1). Specific compounds are described in Examples 1-32. Amonafide is described on column 3, Example 9. Amonafide salt

formed with hydrochloric acid or methansulfonic acid has been described by Brana II (Examples 1-2)

The instant, however, is a carboxylic acid salt, such as tartrate, malonate, citrate, succinate, fumarate or maleate etc (as recited in instant claims 7-9).

Brana does not specifically recite the pharmaceutically acceptable salts since they are well known in the pharmaceutical art, as specifically described by Berge (page 2, Table 1). Zee-Cheng, further exemplifies the suitable acids for salt formation for a similar antitumor naphthalimide (column 1, lines 47-56). Zee-Cheng teaches that hydrochloric acid, methansulfonic acid, tartaric, malonic, citric, succinic, fumaric or maleic acid are all optional choices for making pharmaceutically acceptable salt. Furthermore, Berge teaches that organic acid salts of basic drugs, such as amines, were more soluble in water than the corresponding inorganic (halide) salts (page 7, column 2).

At the time of the invention, one of ordinary skill in the art would be motivated to replace Brana's hydrochloric acid or methansulfonic acid with the alternative organic tartaric, malonic, citric, succinic, fumaric or maleic acid in the preparation of an amonafide salt to arrive at the instant invention, with the reasonable expectation of obtaining an additional pharmaceutically acceptable amonafide salt with a greater solubility for use as an anti-tumor agent.

The comparative data presented in Table 4 (pages 31-32 of the specification) fails to render the instant over the prior art of record for the following reasons. While some of the amonafide organic acid salt of the instant are more soluble in distilled water and in saline at high concentration than the corresponding HCl salt, such a result is not unexpected as it is well recognized in the art that organic acid salts of basic drugs, such as amines, were more soluble in water than the corresponding inorganic (halide) salts (Berge et al. 1977, Journal of Pharmaceutical Sciences, 66(1); 1-19). Indeed, Brana's methansulfonic salt at high concentration is soluble both in saline and distilled water (as shown on page 29 of the specification) and is more soluble than some of the instant carboxylic acid salts. The various carboxylic acid salts of amonafide (tartrate, malonate, citrate, succinate, fumarate or maleate etc) in the Table have similar solubility among themselves, and are similar to the amonafide methansulfonic acid salt of Brana. The instant claims directed to the amonafide carboxylic acid salts or the malic or glycolic acid salts of the non-amonafide compound embraced in the generic claims therefore remain

obvious over the prior art of record since unexpected results have not been established for these claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the amonafide salt compound to treat leukemia, breast, colon, lung or prostate cancer, does not reasonably provide enablement for all the other salt compounds for treating any type of cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to a naphthalimide salt compound for treatment of cancer of all kinds (pages 14-15 of the specification)

b. *State of the prior art and the level of the skilled in the art.*

Naphthalimide compounds similar to the instant are known to be useful for treating leukemia (Brana 5183821, PTO-1449). At present, there is no known drug compound that is effective for all types of cancers.

The level of the skilled artisan in the antitumor art is high.

c. *The predictability/unpredictability of the art.*

The high degree of unpredictability is well-recognized in the antitumor art. A slight change in the structure of the compound would drastically change its biological activity. One of ordinary skill in the art therefore would have no basis to extrapolate the result of the tested compounds to other compounds of dissimilar structures. While amonafide is effective in treating leukemia, and has reproducible minimal activity against B16-melanoma and colon 38 tumor, it is ineffective against other types of tumors (Brana, 5183821, column 6, lines 20-35)

d. *Amount of guidance/working examples.*

Preparation of example compounds is limited to amonafide salts.

The procedures for in vitro cellular proliferation assays in breast, colon, lung or prostate cancer cell lines, in vivo procedures in mice, and the results for amonafide malate, are described on pages 33-38 of the specification and in Figures 2-10.

e. *The breadth of the claim.*

Applicant's assertion that all the structurally diverse compounds (including those wherein R3 and R4 and/or R6 and R7 form a heterocyclic ring of any size having any number of hetero atoms) would be effective for treatment of all types of cancers does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the anti-tumor art, the limited working examples, and the prior art showing that similar naphthalimide compound has little or no anti-tumor activity other than leukemia (paragraphs b-d above).

f. *Quantitation of undue experimentation .*

Since insufficient teaching and guidance have been provided in the specification (paragraphs b-e above), one of ordinary skill in the art, even with high level of skill, would not be able to use the instant compounds as claimed without undue experimentation except for using the amonafide salt compounds to treat leukemia, breast, colon, lung or prostate cancer.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 27 of U.S. Patent No. 6693198 in view of Brana I (4204063, PTO-1449). Although the conflicting claims are not identical, they are not patentably distinct from each other. The patented amonafide malate and amonafide glycolate are encompassed by the instant claims. Amonafide (Brana, column 3, Example 9) has been shown to have anti-tumor activity (Brana, column 1), it is therefore obvious for the skilled in the art to prepare a pharmaceutical composition comprising the patented malate or glycolate salt of amonafide for treating cancer and arrive at the instant invention.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Evelyn Huang
Primary Examiner
Art Unit 1625